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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Paper No. 04092004

Application Number: 09/396,985
Filing Date: September 15, 1999
Appellant(s): BEUTLER ET AL.

Mark B. Wilson
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 10/27/2003.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

The amendment after final rejection filed on 2/21/03 has not been entered.

(5) Summary of Invention

The summary of invention contained in the brief is correct.

(6) Issues

The appellant's statement of the issues in the brief is correct.

(7) Grouping of Claims

The appellant's statement in the brief that certain claims do not stand or fall together is not agreed with because :

With respect to claims 38-40, 52-61, 63-68, 70-75, and 100-103, rejected under 35 U.S.C. 112, second paragraph, claims 39, 40, 57-61 and 100 are not patentably distinct, as argued by Appellant, because claims 39, 40, 57-61 and 100 depend on an indefinite base claim or an indefinite intermediate claim and fail to resolve all the issues which formed the basis of the rejection under 35 U.S.C. 112, second paragraph. For example, claims 39, 57-61, 74 and 100 all depend on rejected base claim 38 and fail to resolve the issue of "lipopolysaccharide mediated response".

With respect to claims 38-40, 52-61, 63-68, 70-75 and 100-103, rejected under 35 U.S.C. 112, first, claims 40, 55 and 56 are not patentably distinct, as argued by Appellant, is agreed with. Appellant's brief includes a statement that claims 40, 55 and 56 are patentably distinct and provides reasons as set forth in 37 CFR 1.192(c)(7) and (c)(8).

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix 2 to the brief is correct.

(9) Prior Art of Record

No prior art is relied upon by the examiner in the rejection of the claims under appeal.

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Rejection under 35 U.S.C. 112, second paragraph,

Claims 38-40, 52-61, 63-68, 70-75 and 100-103 rejected under 35 U.S.C. 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 38, 40 and 52 , 55, 56 and 63-64 are indefinite because the name TLR-4 has not been defined in the claims and specification so as to allow the metes and bounds of the claims to be determined. The specification discloses, page 29, last paragraph, to page 30, "the invention concerns isolated DNA segments and recombinant vectors incorporating DNA sequences that encode a TLR-4 protein or subunit that includes within its amino acid sequence a contiguous amino acid sequence in accordance with, or essentially as set forth in SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:98 or SEQ ID NO:99", Further stated is, "The term, "a sequence essentially as set forth in SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:98 or SEQ ID NO:99", means that the sequence substantially corresponds to a portion of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:98 or SEQ ID NO:99 and has relative few amino acids that are not identical to, or a biological functional of, the amino acids of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:98 or SEQ ID NO:99." Neither the art nor specification discloses the structural and functional properties that

must be present for the polypeptide to be classified as a TLR-4 polypeptide. There is no disclosure of the sequence of amino acids contained in SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:98 or SEQ ID NO:99 that are critical for function. There is no disclosure of which portion of the amino acid sequence of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:98 or SEQ ID NO:99. when contained in a polypeptide would classify it as a TLR-4 polypeptide. The biological function corresponding to a specific portion of the afore mentioned polypeptide is not disclosed. The critical feature of the invention as it relates to structure and function is not disclosed. The name TLR-4 polypeptide encompasses, in view of the specification, modifications and changes which may be made to TLR-4 protein and subunits and still obtain a molecule having like or otherwise desirable characteristics ,see page 73. The structure associated with polypeptide encompassed by the name and the "like or otherwise desirable characteristics" are not disclosed so as to allow the metes and bounds of the claim to be determined. Therefore without a clear disclosure of the structure and associated function of the TLR-4 protein the metes and bounds of the claim cannot be determined.

Claims 38, 40, 52 and 101-103 are indefinite because it is not clear what is encompassed by "mediation of the lipopolysaccharide mediated response" so as to allow the metes and bounds of the claim to be determined. The specification does not provide a clear definition of the "lipopolysaccharide mediated response" and therefore the parameters used to determine the response cannot be determined. The "lipopolysaccharide mediated response" and the parameters screened to determine the response are not defined so as to allow the metes and bounds of the claim to be

determined. Specifically, where does the "lipopolysaccharide mediated response" pathway begin and end so as to allow the metes and bounds of the "lipopolysaccharide mediated response" can be determined

Claims 101-103 are indefinite because it is not clear what is a, "small molecule", so as to allow the metes and bounds of the claim to be determined. The term "small molecule" in claims 101-103 is a relative term, which renders the claim indefinite. The term "small molecule" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. When is molecule considered small as compared to when it is considered big so as to allow the metes and bounds of the claim to be determined. Also what is the boundary when a molecules transitions into a medium or big molecule?

Claims 39, 53-54, 57-61, 65-68, 70-75 are indefinite for depending on a base claim or intermediate claim and fail to resolve the issues raised above.

Claim Rejection, 35 U.S.C. 112

Claims 38-40, 52-61, 63-68, 70-75 and 100-103 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a screening method for compounds which modulate a LPS mediated response by inducing the synthesis or altering expression of TLR-4 of SEQ ID NOs: 2, 4, 6, 98 and 99, does not reasonably provide enablement for other methods of screening for compounds which may affect any other LPS-mediated responses or methods for

identification of compounds which may have other activities by any way other means than the altered expression of TLR-4 (SEQ ID NOs:2, 4, 6, 98 and 99). The, specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims are directed to screening for modulators of a LPS mediated response. The specification discloses that TLR-4 mRNA is induced by LPS (Fig 9) and TLR4 is the limiting factor in LPS signal transduction in LPS responsive macrophages, the quantity of TLR4 expressed is an important limiting factor in the intensity of the signal that is evoked (page 128). The specification discloses the screening of modulators of LPS mediated response where the compounds screened can modulate the expression of TLR-4 of SEQ ID NOs:2, 4, 6, 98 and 99. The scope of the claims which encompasses other methods of screening for modulators of LPS, using proteins other than those disclosed in SEQ ID NOs:2, 4, 6, 98 and 99, where the compounds may have activity by other means than the altered expression of TLR-4 expression of SEQ ID NOs:2, 4, 6, 98 and 99 is not enabled by the disclosure. For the person of ordinary skill in the art to screen for modulators of a LPS mediated response by any other means than those disclosed as "enabling" above, the artisan must first isolate other proteins capable of direct or indirect interaction with LPS and its modulators, and develop screening assays to determine if certain compounds can be modulators of the LPS mediated response. Therefore, the lack of guidance provided in the specification as to what other assays may be used to screen for modulators of LPS (see rejection under 112, second

paragraph disclosing the difficulty in determining what is the scope of the lipopolysaccharide mediated response), unpredictability and undue experimentation in isolating other TLR-4 polypeptides would prevent the skilled artisan from practicing the invention in its full scope.

(11) Response to Argument

(A) The Claims are Definite Under 35 U.S.C. § 112, Second Paragraph

(i) Appellants' arguments pertaining to the term TLR-4 being insufficiently defining of the TL4-polypeptide of the invention are summarized below:

Appellants argue that Appellants have defined the term TLR-4 in light of the specification and the skill of the ordinary artisan. Appellants argue that a detailed and consistent definition of TLR-4 is provided in the specification, most particularly, TLR-4 as used by the Appellants in describing particular embodiments refers explicitly to polypeptides of the sequence of SEQ ID NO:2, 4, 6, 98 or 99 and those sequences at least about 85% similar thereto or biologically functional equivalents thereof. Also, Appellants argue the specification discloses structural and functional properties of TLR-4 and methods by which a TLR-4 mediated response to LPS can be assayed.

Appellants argue the term TL4-4 is well known to those skilled in the art and a list of references in the art using TLR-4 to refer to the polypeptides as the Appellants have defined them in the specification is attached as Exhibit B, and the Declaration of Dr. Davis D. Chaplin states that the specification as filed provides

sufficient structural and functional properties by which to identify a protein as TLR-4 or its homolog.

Appellants arguments and the declaration of Dr. Davis D. Chaplin have been fully considered and not found persuasive for the reasons given below:

The name TLR-4 has not been defined in the claims and specification so as to allow the metes and bounds of the claims to be determined. Appellants argue TLR-4 has been defined to meet the requirement of 35 U.S.C. § 112, Second Paragraph. The specification discloses, page 29, last paragraph, to page 30, "the invention concerns isolated DNA segments and recombinant vectors incorporating DNA sequences that encode a TLR-4 protein or subunit that includes within its amino acid sequence a contiguous amino acid sequence in accordance with, or essentially as set forth in SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:98 or SEQ ID NO:99", Further stated is, "The term, "a sequence essentially as set forth in SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:98 or SEQ ID NO:99", means that the sequence substantially corresponds to a portion of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:98 or SEQ ID NO:99 and has relative few amino acids that are not identical to, or a biological functional of, the amino acids of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:98 or SEQ ID NO:99." Neither the art nor specification discloses the specific structural and functional properties that must be present for the polypeptide to be classified as a TLR-4 polypeptide. There is no disclosure of the sequence of amino acids contained in SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:98 or SEQ ID NO:99 that are critical for function. There is no disclosure of which portion of the

amino acid sequence of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:98 or SEQ ID NO:99. when contained in a polypeptide would classify it as a TLR-4 polypeptide. The biological function corresponding to a specific portion of the afore mentioned polypeptide is not disclosed. The critical feature of the invention as it relates to structure and function is not disclosed. Chaplin discusses the general function of TLR-4 proteins and their primary role in mediating responses to endotoxins but does not specifically define the TLR-4 protein. For example, if a protein is provided to an artisan, what specific structural and specific functional features allow for its classification as a TLR-4 peptide. No disclosure is provided as to the critical structural feature of the invention that is responsible for a specific endotoxin signaling. Pertaining to function, all proteins that mediate endotoxin response are not classified as TLR-polypeptides, absent evidence to the contrary. Pertaining to structure, although Table V provides examples of homology profiles, from different species, of some polypeptides classified as TLR-4, there is no disclosure of what specific structural features define a TLR-4 protein or polypeptide. A mere comparison of polypeptides is not a definition. All proteins that show some sequence similarity to those disclosed in Table V are not classified as a TLR-4 . The name TLR-4 polypeptide encompasses, in view of the specification, modifications and changes which may be made to TLR-4 protein and subunits and still obtain a molecule having like or otherwise desirable characteristics ,see page 73. The structure associated with polypeptide encompassed by the name and the "like or otherwise desirable characteristics" are not disclosed so as to allow the metes and bounds of the claim to be determined. Therefore without a clear disclosure

of the structure and associated function of the TLR-4 protein the metes and bounds of the claim cannot be determined. Further, post filing art cannot be used to define the TLR-4 polypeptide.

Appellants argue the rejection under 35 U.S.C. § 112, Second Paragraph, of claims 39, 40, 57-61, 74 and 100, as pertaining to "the name TLR-4 has not been defined in the claims and the specification so as to allow the metes and bounds of the claim to be determined" cannot be applied to said claims because these claims implicate the amino acid structure of TLR-4 polypeptide. Appellants' arguments have been fully considered and found persuasive.

(ii) Appellants arguments pertaining to the phrase "lipopolysaccharide mediated response" is unclear and are summarized below:

Appellants argue lipopolysaccharide mediated response is well known in the art and draw attention the specification beginning at line 19 of page 2 and extending through line 5 of page 3. TLR-4 is stated to be the LPS (endotoxin) receptor. Appellants argue the declaration of Dr. Chaplin has been improperly misquoted. Appellants argue the Action quotes the specification out of context when only quoting the last sentence of the last paragraph on page 3, and provides the whole paragraph. Appellants argue the Medical Microbiology, 4th ed. 1996 provides extensive literature on lipopolysaccharide mediated response and thus, LPS-mediated response at least include those activities listed in Table 7-4, page 132.

Appellants' arguments have been fully considered and not found persuasive for reason given below:

It is not clear what is encompassed by "lipopolysaccharide mediated response" mediated by TLR-4 so as to allow the metes and bounds of the claim to be determined. The specification, Declaration of Dr. Chaplin, Medical Microbiology, 4th ed. 1996 all provide examples of examples of what may be considered a LPS response, but no definition of a lipopolysaccharide response mediated by TLR-4 polypeptide. Dr. Chaplin argues against the Examiners assertion that the "lipopolysaccharide mediated response" is not clearly defined by stating, I do not find this to be the case" and further discloses, "the actors and elements of lipopolysaccharide mediated response that are mediated by TLR-4 are disclosed in the specification". Dr. Chaplin does not provide a definition of "lipopolysaccharide mediated response" mediated by TLR-4. Disclosing examples of the "lipopolysaccharide mediated response", or that the response is well known does not define which lipopolysaccharide mediated responses are mediated by TLR-4. Since TLR-2 also has been suggested to partially mediate the lipopolysaccharide induced cellular signaling, see page 4 of specification, first paragraph, it is not clear what responses considered as "lipopolysaccharide mediated response", are mediated by TLR-4 as compared to other polypeptide/proteins which may effect lipopolysaccharide induced cellular signaling. Although Appellants argue the prior Office Action quotes the specification out of context when only quoting the last sentence of the last paragraph on page 3, Examiner disagrees. The last part of the paragraph in question clearly discloses the state of the art as pertaining to defining

lipopolysaccharide mediated response mediated by TLR-4, and states, "But the initial controlling element and event in the signaling pathway of macrophage response to endotoxins has not been defined. Thus, in spite of its importance most of the endotoxin signaling pathway remains relatively unknown". If most of the pathway remains relatively unknown providing examples of "lipopolysaccharide mediated response", which may be mediated via TLR-2, TLR-4 or some other protein does not define the "lipopolysaccharide mediated response", mediated by TLR-4 so as to allow the metes and bounds of the claim to be determined.

The specification does not provide a clear definition of the "lipopolysaccharide mediated response" mediated by TLR-4 and therefore the parameters used to measure the response cannot be determined. The "lipopolysaccharide mediated response" and the parameters screened to determine the response are not defined so as to allow the metes and bounds of the claim to be determined. Specifically, where does the "lipopolysaccharide mediated response" pathway begin and end so as to allow the metes and bounds of the "lipopolysaccharide mediated response" can be determined

(iii) Appellants' arguments pertaining to the phrase "small molecule" is indefinite are summarized below:

Appellants argue the term "small molecule inhibitor" has a well established meaning in the art and provides the declaration of Dr. Chaplin as support for the term being a definition accepted in the art.

Appellants arguments have been fully considered and not found persuasive for reason given below:

It is not clear what is a, "small molecule", so as to allow the metes and bounds of the claim to be determined. Applicants have not specifically addressed the examiner's rejection. The term "small molecule" in claims 101-103 is a relative term, which renders the claim indefinite. The term "small molecule" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. When is molecule considered small as compared to when it is considered big so as to allow the metes and bounds of the claim to be determined. Also what is the boundary when a molecules transitions into a medium or big molecule? The Declaration of Dr. Chaplin, prior art nor the specification provides a definition when a molecule is considered to be small. Further finding a use of a term in the prior art does not necessarily overcome the rejection of record. Therefore without a clear definition of "small molecule" the rejection is maintained.

(B) The Claims are enabled Under 35 U.S.C. § 112, first Paragraph

(i) Appellants arguments pertaining to: a) legal standard of enablement, b) action supplies no factual or scientific principle to reasonably doubt appellants' disclosure, c) action misconstrues the invention in asserting lack of enablement.

Appellants contend that the Examiner has not carried the burden of establishing a *prima facie* case of lack of enablement and misconstrues the invention in asserting lack of enablement. Appellants state The Action demands that the method disclose

"how the modulator targets a TLR-4 polypeptide and if the response being measured is in fact a lipopolyscccahride mediated response, since there are no controls to compare the results to". Appellants argue that the pending claims are directed to methods of screening for modulators of a lipopolysaccharide mediated response that compare the response before and after contact of TLR-4 with a putative modulator or candidate compound. As such, the method does not require that the exact nature of action of any successful modulator so identified be determined prior to the screening procedure. If the artisan knew the identity of the modulator and its mode of action, there would be no need to practice the present invention. Appellants also argue the nature and scope of a lipopolysaccharide-mediated response is clear to the artisan and the claims specify the comparison between the measured LPS response prior to the contact with TLR-4 by the modulator with the measured LPS response after contact with TLR-4 by the putative modulator, wherein a difference in the lipopolysaccharide mediated response indicates that the putative modulator is a modulator of a lipopolyscaccharide response.

Appellants' arguments have been fully considered but not found persuasive. The claims are directed to screening for modulators of a LPS mediated response mediated by the TLR-4 polypeptide. The method requires that the exact nature of action of any successful modulator so identified be determined by measurement of a specific lipopolysaccharide mediated response mediated by the TLR-4 polypeptide. Claims 38, 39, 40, 52-61, 65-75, 100-103 are not limited to a specific lipopolysaccharide response mediated by the TLR-4 polypeptide. Claims 38, 52,-56, 63-73, 75, 101-103 are not limited to a specific defined TLR-4 polypeptide. As

disclosed above ,neither the specification nor prior art provide a clear definition of the "lipopolysaccharide mediated response" by TLR-4 polypeptide and therefore the parameters used to measure the response cannot be determined. Specifically, where does the "lipopolysaccharide mediated response" mediated by TLR-4 pathway begin and ends? The claims require the measurement of a specific lipopolysaccharide mediated response by the TLR-4 polypeptide. For the claim to be enabled in its full scope the response has to be measured. If the response is not known, how can it be measured. Further without a control assay any response measured may be as a result of modulators acting on some other polypeptide e.g. TLR-2 (suggested to partially mediate LPS-induced cellular signaling, see page 2, specification), and therefore the LPS mediated response would not be through TLR-4. Therefore to practice the invention the identity of the modulator may be unknown but its mode of action must be determined by measurement of a specific LPS mediated response mediated by TLR-4. The nature and scope of a lipopolysaccharide-mediated response is not clear to the artisan because a comparison between the measured LPS response prior to the contact with TLR-4 by the modulator with the measured LPS response after contact with TLR-4 by the putative modulator would not necessarily indicate that the putative modulator is a modulator of a lipopolyscaccharide response mediated by TLR-4 because there is no control assay. It must be noted that a cell expressing TLR-4 also expresses other polypeptides which may also mediate a lipopolyscaccharide response. Further as disclosed above the name TLR-4 does not provide a clear definition of the structure and associated function of the TLR-4 protein and therefore it is not clear what TLR-4 is

encompassed by the and claim what lipopolysachharide mediated response is mediated by undisclosed TLR-4.

(ii) Appellants arguments pertaining to: a) unsupported, or unsupportable allegations do not rise to the level of factual evidence or scientific principle, b) appellants supply abundant factual evidence of enablement, c) the action misconstrues the invention and appellants arguments, d) claims 40/55 and 56 are separately patentable.

Appellants argue that the allegation that the LPS-mediated response mediated by TLR-4 could be due to some other pathway simply ignores the nature of Appellants discoveries and the extensive disclosure provided regarding the central, indispensable role of TLR-4 polypeptide in LPS-mediated responses. Appellants further argue, although altering expression of TLR-4 of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:98 or SEQ ID NO:99" may be one mode of LPS response measured the specification provides description of the events and circumstances that comprise the induction of a response to LPS and the resultant effects that may be measured as indicative of a LPS-mediated response and all these responses may be utilized in the practice of the presently claimed methods by those of skill in the art.

Appellants' arguments have been fully considered but not found persuasive. The claims contain the limitation of "measuring a lipopolysaccharide mediated response mediated by TLR-4 polypeptide" before and after contact with a putative modulator. The claims are directed to screening for modulators of a LPS mediated response

mediated by the TLR-4 polypeptide. The method requires that the exact nature of action of any successful modulator so identified be determined by measurement of a specific lipopolysaccharide mediated response mediated by the TLR-4 polypeptide. Claims 38, 39, 40, 52-61, 65-75, 100-103 are not limited to a specific lipopolysaccharide mediated response mediated by the TLR- polypeptide. Claims 38, 52,-56, 63-73, 75, 101-103 are not limited to a specific defined TLR-4 polypeptide. As disclosed above neither the specification nor prior art provide a clear definition of the "lipopolysaccharide mediated response" by TLR-4 polypeptide and therefore the parameters used to measure the response cannot be determined. Specifically, where does the "lipopolysaccharide mediated response" mediated by TLR-4 pathway begin and end? The claims require the measurement of a specific lipopolysaccharide mediated response by the TLR-4 polypeptide. For the claim to be enabled in its full scope the response specific to TLR-4 modulation has to be measured. Further without a control assay any response measured may be as a result of modulators acting on some other polypeptide e.g. TLR-2 (suggested to partially mediate LPS-induced cellular signaling, see page 2, specification), and therefore the LPS mediated response would not be through TLR-4. Therefore to practice the invention the identity of the modulator may be unknown but its mode of action must be determined by measurement of a specific LPS mediated response mediated by TLR-4. The claims require a lipopolysaccharide-mediated response be measured prior to the contact of TLR-4 by the modulator and compared with the measured LPS response after contact of TLR-4 by the putative modulator (both in a cell expressing TLR-4 polypeptide). The difference

in the lipopolysaccharide mediated response measured would not necessarily indicate that the putative modulator is a modulator of a lipopolyscaccharide response mediated by TLR-4 because there is no control assay. It must be noted that a cell expressing TLR-4 also expresses other polypeptides which may also mediate a lipopolyscaccharide response. Therefore a LPS response measured before contact with modulator may be through TLR-2. For example, the LPS response measured after exposure with modulator may be through TLR-2. Comparing the LPS mediated response before and after exposure to modulator does not necessarily show the LPS mediated response is mediated by TLR-4 polypeptide. Further as stated above, the name TLR-4 does not provide a clear definition of the structure and associated function of the TLR-4 protein and therefore it is not clear what TLR-4 is encompassed by the claim or what lipopolysachharide mediated response is mediated by undisclosed TLR-4. As pertaining to enablement of claims 40, 55 and 56, the claims do not disclose the promoter for a TLR-4 gene, the reporter gene and what it reports.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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April 15, 2004

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